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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,814	07/26/2001	Madeline M. Butler	ISPH-0587	6393

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EXAMINER

ZARA, JANE J

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/915,814

Applicant(s)

BUTLER ET AL.

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-15 and 76-83 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-15 and 76-83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 5-17-05.

Claims 1, 2, 4-15, 76-83 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejection not repeated in this Office action is hereby withdrawn.

Maintained Rejections

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth in the Office actions mailed 3-24-04 and 11-17-04.

Applicant's arguments filed 5-17-05 have been fully considered but they are not fully persuasive. Applicants argue that undue experimentation is not required by one of skill in the art to identify antisense compounds, in addition to SEQ ID NO: 179, that would inhibit HSL in vivo. Applicants also argue that Examples 19-24 of the instant specification provide working examples demonstrating that antisense oligonucleotides reduce target gene (HSL) expression in vivo and elicit a variety of desired biological responses, including reduction in blood glucose levels, reduction in liver weight without affecting fat weight, reduction in serum insulin levels, and reduction in liver enzyme AST and ALT levels, and reduction in serum cholesterol and triglyceride levels. Applicants also argue that the specification provides a large number of compounds (e.g. in Table 2,

pages 89-90 of the instant specification) that have been designed to target and inhibit human HSL, that have been found amenable to cellular uptake, target binding and inhibition of target gene expression.

Applicants are correct that the specification discloses numerous antisense oligonucleotides that have been found to specifically target and inhibit the expression of human HSL (of SEQ ID NO: 3) in target cells in culture. Applicants are also correct that in vivo target gene inhibition and the various biological effects described above have been shown for the single antisense oligonucleotide of SEQ ID NO: 179. But, contrary to Applicants' assertions, the successful in vitro targeting of cells by various antisense and the in vivo efficacy of a single antisense oligonucleotide do not provide adequate guidance for the full scope claimed. The invention is enabled for the scope claimed as it pertains to SEQ ID NO: 179. The in vivo success of one antisense, however, does not represent the in vivo success of any antisense oligonucleotide that targets SEQ ID NO: 3. The in vitro results (e.g. illustrating adequate cellular uptake and subsequent inhibition of target gene expression for the various antisense sequences disclosed) were obtained under experimental conditions that do not accurately mimic or reflect in vivo conditions (e.g. the oligonucleotide concentrations exposed to target cells in culture are not uniformly achieved in vivo.) The concentration achieved in vivo will depend on various factors, including the type of target cell harboring the target gene to be silenced, as well as antisense stability and target gene binding to the appropriate target region. The in vivo efficacy achieved using one antisense oligonucleotide is not correlative or representative of the ability to achieve such efficacy using a different and distinct

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antisense, targeting a different portion of the target gene sequence. And the in vitro results are not predictive of in vivo efficacy. For these reasons, the instant rejection for lacking enablement over the scope claimed is maintained.

Rejections Necessitated by Amendments.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 4-14, 76-83 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Baker et al.

Baker et al (USPN 6,080,580) teach compositions comprising an antisense oligonucleotide, or mimetic thereof, between 8-50 nucleobases that specifically hybridizes with nucleotides 1-970 of SEQ ID NO: 3, encoding human hormone sensitive lipase (hHSL) and inhibits its expression in vitro, which antisense oligonucleotide

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comprises phosphorothioate internucleotide linkages, 5-methyl cytosine and 2'-O-methoxyethyl sugar moieties, and optionally comprises chimeric oligonucleotides, and which composition comprises a pharmaceutically acceptable diluent and a colloidal dispersion system (see SEQ ID NO: 110 of Holly, and the accompanying sequence alignment data, which is attached to the Office action; see also col. 8-12 and col. 15-16).

The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. The sequence cited above that shares less than 100% homology with the target gene (see accompanying alignment data illustrating 100% homology for 12 out of 15 nucleotides) is presumed to have inhibitory function

since sequences with less than 100% homology meet the structural requirements of the claimed invention as indicated in the instant specification under the discussion of "specifically hybridizing." (e.g. page 9, line 9-page 10, line 6 of the instant specification). Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Baker et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically inhibiting expression hHSL in HepG2 cells in vitro as claimed.

Therefore, absent evidence to the contrary, claims 1, 2, 4-14, 76-83 are anticipated by or, in the alternative, obvious over Baker et al.

Claims 1, 2, 11-13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Couture et al.

Couture et al (USPN 5,705,388) teach an antisense oligonucleotide between 8-50 nucleobases that specifically hybridizes with nucleotides 1-970 of SEQ ID NO: 3, encoding human hormone sensitive lipase (hHSL) and inhibits its expression in vitro (see SEQ ID Nos: 161 and 162 and the accompanying sequence alignment data, which is attached to the Office action).

The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or

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substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. The sequence cited above that shares less than 100% homology with the target gene (see accompanying alignment data illustrating 100% homology for 13 out of 20 nucleotides) is presumed to have inhibitory function since sequences with less than 100% homology meet the structural requirements of the claimed invention as indicated in the instant specification under the discussion of "specifically hybridizing." (e.g. page 9, line 9-page 10, line 6 of the instant specification). See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594, 596 (CCPA 1980), quoting *In re Best* 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Couture et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically inhibiting expression hHSL in vitro.

Therefore, absent evidence to the contrary, claims 1, 2, 11-13 and 14 are anticipated by or, in the alternative, obvious over Couture et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-15 and ⁷⁶⁻~~72~~-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holly, Strosberg, Langin and Holst, the combination in view of Milner et al and McKay, the combination in view of Laurell et al and Kosaki et al insofar as the claims are drawn to compositions and methods comprising the administration of antisense oligonucleotides between 8 and 50 nucleobases in length that specifically target hHSL of SEQ ID NO: 3 (and including those antisense oligonucleotides that specifically target the region of nucleotides 1-970) and inhibit hsl expression (e.g. by at least 5%) in 80% confluent HepG2 cells in culture, and which antisense comprise phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugar moieties, 5-

methycytosine, or which antisense are optionally chimeric, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Holly et al (USPN 5,502,034) teach an antisense oligonucleotide between 8-50 nucleobases that specifically hybridizes with SEQ ID NO: 3, encoding human hormone sensitive lipase (hHSL) and inhibits its expression in vitro (see SEQ ID NO: 5 of Holly).

Strosberg et al (WO 96/34100) teach an antisense oligonucleotide between 8-50 nucleobases that specifically hybridizes with SEQ ID NO: 3, encoding human hormone sensitive lipase (hHSL) and inhibits its expression in vitro (see Accession No. AAT43117, example 1 on p. 17).

Holst et al (Holst, L. S. et al, Genomics 35: 441-447, 1996) teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3. Holst et al also teach hsl as an important regulator of energy homeostasis, which is poorly understood (See the first paragraph on p. 441, and the fourth full paragraph on p. 442).

Langin et al (Langin, D. et al., Proc. Natl. Acad. Sci, USA, 90: 4897-4901, 1993) teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3. Langin et al also teach the potential role of hsl in pathophysiological states including obesity and diabetes as a motivation to study this molecule (See second full paragraph in right hand column on p. 4897, second and fourth full paragraphs on p. 4898; see also Accession No. 711706, deposited by Langin et al to Genbank, encoding hsl).

The primary references of Holly, Strosberg, Holst and Langin do not teach the inhibition of hsl expression by targeting the first 900-1000 nucleotides of the coding region of SEQ ID NO: 3 in HepG2 cells in vitro, nor the incorporation of modified internucleotide, sugar or nucleobase modifications into antisense, nor the use of chimeric oligonucleotides nor compositions comprising colloidal dispersions.

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence in vitro (See especially figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which compositions further comprise a colloidal dispersion system and a pharmaceutically acceptable carrier. McKay et al also teach the in vitro inhibition of various antisense oligonucleotides between 8-50 nucleobases that specifically hybridize with the target gene, and which antisense target the 5', coding and 3' regions of the target gene of interest (see especially col. 6, line 29 through col. 15, line 10; col. 20, line 18 through col. 24, line 67; see also Tables 2 and 3 in col. 37-38).

Laurell et al (Biochem. J., 328: 137-143, 1997) teach that hsl catalyzes the rate limiting step of adipose tissue lipolysis, and that hsl is a critical enzyme in fat and

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energy accumulation in the body (first paragraph of the introduction, p. 137). Laurell et al teach the ability of insulin to antagonize hormone induced lipolysis by decreasing cAMP levels and activating phosphodiesterases (first paragraph of the introduction, p. 137). Laurell et al additionally teach the regulation of hsl via its phosphorylation (*id.*) and that hsl is under hormonal regulation (*id.*).

Kosaki et al (J. Biol. Chem., 270(35): 20,816-20,823, 1995) teach the use of HepG2 cells as a model cell line because it is one of the major sites of insulin action (second paragraph of the introduction on page 20,816). Kosaki et al also teach the B isoform of insulin to have greater insulin stimulated kinase activity (last paragraph on page 20,823).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of hsl of SEQ ID NO: 3 in vitro, because Milner et al and McKay teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15). In addition, Langin et al teach the nucleotide sequence of the target hsl gene and Strosberg et al teach antisense that specifically target hsl of SEQ ID NO: 3, and inhibit the in vitro expression of hsl of SEQ ID NO: 3. One of ordinary skill in the art would have been motivated to inhibit the expression of HSL in vitro by targeting the first half of the coding region (e.g. nucleotides 1-970) because many in the field, including Milner and McKay, teach the targeting of various regions of a target gene of known sequence, including the 5', coding

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and 3' regions of the known target gene sequence. One of ordinary skill in the art would have been motivated to inhibit the expression of HSL in vitro to study its role in diabetes and obesity, as taught by Langin, and to study the effect on lipolysis because this enzyme is known to catalyze the rate limiting step in adipose lipolysis, and is critical in fat and energy accumulation in the body, as taught previously by Laurell et al. One of ordinary skill in the art would have been motivated to inhibit hsl expression using antisense in HepG2 cells in vitro because HepG2 cells have been utilized historically to study the effects of insulin action on various aspects of cellular metabolism, and these cells therefore are appropriate to study the involvement of insulin in regulating HSL, and to study the effects of insulin on the process of lipolysis (e.g. when HSL expression is inhibited in such model cells). It would have been obvious to one of ordinary skill in the art to inhibit the expression of the hsl nucleic acid of known nucleotide sequence (e.g. SEQ ID NO: 3) in vitro using antisense oligonucleotides because the methods for inhibiting a target gene of known sequence using antisense had been taught previously by Milner et al and such methods of screening antisense in vitro for inhibition of target gene expression were routine at the time the invention was made. Milner et al additionally teach methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. McKay et al also teach the routine screening of specific antisense oligonucleotides for their ability to inhibit the expression of their corresponding target gene in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of

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known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 8-50 nucleobases) for the in vitro inhibition of hsl expression of SEQ ID NO: 3. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have been motivated to utilize pharmaceutically acceptable diluents in order to achieve the appropriate concentration of antisense oligonucleotides for administration to target cells in a manner which is compatible for maintaining cellular integrity and antisense stability and one would have been motivated to utilize colloidal dispersions in order to enhance antisense stability and cellular delivery of antisense, as taught by McKay et al. One of ordinary skill in the art would have expected that the delivery of modified antisense (mimetics) to target cells harboring hsl, including HepG2 cells, which antisense specifically hybridize with the target nucleic acid encoding hsl (i.e. of SEQ ID NO: 3), would lead to inhibition of expression of hsl in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-15, 76-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims comprise limitations of the target region of SEQ ID NO: 3 comprising "nucleotides 1 through 970" (e.g. line 3 of claim 1, lines 2-3 of claim 11, line 2 of claim 76). It is unclear where support is provided for this limitation in the original specification or claims. Applicant is requested to provide support for such limitations in the instant disclosure.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**, or after July 15, 2005, the new fax telephone number is

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571-273-8300. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED** so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
7-26-05

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TC1600